Author’s response to reviews

Title: The public health impact of malaria vaccine RTS,S in malaria endemic Africa: country-specific predictions using 18 month follow-up Phase III data and simulation models

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*Revision of manuscript: The public health impact of malaria vaccine RTS,S*

Dear BMC Medicine,

We would like to thank you for the review of our manuscript “The public health impact of malaria vaccine RTS,S in malaria endemic Africa: country-specific predictions using 18 month follow-up Phase III data and simulation models” and for giving us the opportunity to revise the manuscript for publication in BMC Medicine.

A detailed point-by-point response to each of the reviewers’ comments is included below. Included with this revision are new drafts of the manuscript and supplementary information, and versions of these documents with full Track Changes.

Best regards,

Melissa Penny and Tom Smith

(Swiss Tropical and Public Health Institute)
Referee 2

We thank the reviewer for their helpful comments and hope they are satisfied with the point-by-point responses below.

The authors’ responses are mostly adequate. A few remaining minor points:

1) “Due to availability of site- and time-specific data from Phase II, we restrict trial data to Phase III sites using adjuvant AS01”.
   Should be: “Due to an absence of …”?
   
   This was an error, now corrected

2) “Repeated malaria infections induces natural, but not complete, immunity in the host to all stages of the parasite life-cycle, including the blood stage causing clinical disease.”
   This is a potential controversial statement. Whether or not, even partial immunity (i.e., protective immune response) against liver stages is being induced by natural infections remains an open question. I recommend to rephrase slightly to emphasise the massive evidence for partial immunity against blood stages.
   
   This has been updated in the introduction to emphasise blood-stage immunity

3) Fig. SM1a, right panel: “Burden in cohort with with no vaccine”
   Remove one ‘with’ Also, I’m not sure whether I understand what the red blocks labeled “vaccine modified burden…” on an age vs time plot are supposed to indicate…
   
   Correction made. The red represents the vaccinated cohort the observed burden in those age groups, which is modified, compared to non-vaccinated cohorts. We have made this clearer by indicating equivalent in the right panel (non-vaccinated cohort) and changing the figure legend text.

4) Fig. SM1b: why is the number of total events AVERTED including the burden in non-vaccinated ages over time? Are the authors referring to a potential excess burden in the non-vaccinated groups?
   
   Sorry, we did no mean to imply we referring to excess burden in the non-vaccinated ages. For population projections over 5, 10 and 15 years, we account for total burden across all ages, even those non-vaccinated at any time. We do this in the vaccinated simulations, and the baseline simulations of no vaccine so as to calculate total events averted (being the difference between the two). The figure legend was updated to reflect this.

5) "We didn’t address co-administration, interaction with hep b explicitly, but did briefly address maternal immunity."
   This left me wondering whether my question was unclear… my original point has been to provide an elegant explanation for the differential effects in the 6-12 week vs 5 to 17 months cohort. The authors repeatedly mention the ‘age shifting of susceptibility’ … predicting that vaccine induced protection is more difficult to prove in children who are in the process of acquiring partial immunity. Now, 6-12 week old infants are ‘natural recipients’ of maternally transmitted antibodies (that are slowly decaying over the first year of life) and so represent a mirror-image of the immunological situation of children slowly acquiring immune responses…extending (or rather, reversing?) the ‘age shifting of susceptibility’ paradigm to the younger cohort may therefore be useful.
   
   The reason for reduced efficacy in the younger cohort likely relates to maternal immunity, but that does not "represent a mirror-image of the immunological situation of children slowly
acquiring immune responses”. The models consistently indicate that the effectiveness of the vaccine will be less in groups with more pre-existing immunity. This is because the pre-existing immunity introduces additional non-linear effects that can attenuate the vaccine effect, but are unlikely to enhance it (because the vaccine does not boost natural immune responses).

We could introduce text to this effect but fear that this would unduly complicate the paper. None of this, however, is essential for rapid publication.